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Paediatric neurology: advances on many fronts

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Paediatric neurology is sometimes regarded as a sub-speciality that involves diagnosis of rare disorders but specialists are rarely able to provide curative treatment. Neurological disorders in children are common, particularly in developing countries where these conditions cause substantial mortality and long-term morbidity. In 2008, epidemiological studies have dispelled spurious associations and have provided the estimated burden of paediatric disorders. Other studies have rapidly used advances in the basic sciences to provide novel insights into neurological disorders and clinical trials have improved the outcome of severe neurological conditions.

Febrile seizures are the most common paediatric neurological condition, occurring in 2–5% of children. The link between febrile seizures and sudden infant death is controversial; aetiological, environmental, and genetic factors are thought to be similar in both disorders. However, in a nationwide Danish study, no association between febrile seizures and sudden infant death was found¹ and the prognosis of febrile seizures was confirmed to be good, provided there was no underlying neurological condition or the seizures were not complex.

Although status epilepticus is the most common neurological emergency in children, little is known about the epidemiology, causes, and outcome. Until a recent study in London, UK,² there were few epidemiological studies of convulsive status epilepticus in children. The incidence in London was found to be 20 out of 100 000, of which 32% were febrile seizures and 6% were pyogenic meningitis, with an overall acute mortality of 3%. A study of the incidence of status epilepticus in Kenya shows that the situation in resource-poor regions is startlingly worse.³ Definite and probable cases were eight times the incidence of that of the London study, as ascertained by hospital admission, but this calculation is probably an underestimation because many children die before reaching hospital. Overall, 15% of patients died in hospital, 21% died during follow up, and 12% had neurological sequelae. Prevention of this poor outcome is possible because 71% of cases have an infective cause (53% malaria, 11% bacteraemia, and 9% acute bacterial meningitis, with overlap between these conditions). This study highlights a major treatment gap in the management of infection-related prolonged seizures in countries that have limited resources. Both the primary prevention of infections and acute treatment could help to reduce the number of casualties to a level that is similar to that of higher income nations.

The ketogenic diet has been used for more than 50 years in epilepsy, but until recently no randomised clinical trials had been done in children. In a randomised trial in 2008, the efficacy of the ketogenic diet was of similar magnitude to that of currently used antiepileptic drugs when used as add-on therapy: 38% had a more than 50% decrease in seizure frequency, although seizure freedom was rare and a decrease in seizures by more than 90% was uncommon (7%).⁴ This trial enrolled a group of patients with particularly intractable forms of epilepsy and several severe epilepsy syndromes and investigated both a classic and

a medium chain triglyceride diet. Only 103 of the original 145 recruited patients completed the trial, but only six dropped out because of poor tolerance of the diet. Nearly a half had gastrointestinal side-effects (vomiting, diarrhoea, abdominal pain, and hunger) and a third had constipation, which emphasises the importance of a dietician being available for regular consultation. The authors of the study point out some limitations of the trial, such as absence of blinding of the observers; however, the practical difficulties of undertaking such a study mean that it is unlikely to be repeated.

Menkes disease is a rare disorder of copper metabolism that leads to a fatal neurodegenerative disorder in early childhood. This disease is caused by diverse mutations in the copper transport gene *ATP7A*. Early treatment might prevent death, but early diagnosis is difficult. The results of a study of children at risk of developing Menkes disease showed that measurement of dopamine and dihydroxyphenylacetic acid in the plasma could be used to identify children who developed Menkes disease.⁵ Furthermore, early treatment with intravenous copper significantly decreased mortality and improved neurodevelopmental outcome compared with historical controls. Finally, the results from this study showed that infants who had mutations that do not completely interfere with the function of *ATP7A* are particularly responsive to early copper treatment.

In 2008, the Nobel prize for Chemistry was awarded to the discoverers of the green fluorescent proteins; therefore, it is timely to highlight the use of this discovery in providing insights into neurological conditions. Rett syndrome occurs in girls and is characterised by initial normal development, followed by the loss of developmental milestones and a decrease in head growth, as well as hand wringing, seizures, and episodes of hyperventilation and apnoea. The syndrome is caused by a variety of mutations in the gene that encodes methyl-CpG-binding protein-2 (*MeCP2*), which leads to a spectrum of phenotypes. In a mouse model in which an enhanced green fluorescent protein is inserted into the *mecp2* locus, a fusion form of *MeCP2* that has the same expression and

functionality as the parent protein can be expressed.⁶ This model has the potential to provide further insights into the clinical range of the phenotypes of Rett syndrome and possible pharmacological interventions.

These papers indicate the extent of paediatric neurological conditions and highlight the advances made in all areas of this specialised field.

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